STUDY OF HELICOBACTER PYLORI IN TYPE 2 DIABETES MELLITUS PATIENTS WITH DYSPEPSIA

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CERTIFICATE

This is to certify that this dissertation entitled **"Study of Helicobacter pylori in Type 2 diabetes mellitus patients with dyspepsia"** Submitted by **Dr.T.ARUN to** the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfilment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

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CONTENTS

Study of Helicobacter pylori in Type 2 diabetes mellitus patients with dyspepsia

AIM

The aim of the study was to determine the frequency of Helicobacter pylori (H. pylori) infection in Type 2 diabetic and non-diabetic patients with dyspepsia.

MATERIALS AND METHODS

This was a prospective case control study done in Department of Digestive Health and Diseases(DDHD),Government peripheral hospital,Annanagar,Chennai.A total of 100 patients with 50 in each arm were included in the study protocol.Upper gastrointestinal endoscopy was done with biopsies taken from antrum and body of stomach.The biopsy samples were subjected to rapid urease test and routine histopathology. For all Type 2 diabetic patients, HbA_1c, Fasting and Post prandial blood sugar were done.

RESULTS

Our study showed 40/48(83.3%) patients were rapid urease test positive for helicobacter pylori infection as compared to 22/47(46.8%) of rapid urease test positive for helicobacter pylori infection in non diabetic controls proving that infection with helicobacter pylori is increased in Type 2 diabetics with dyspepsia which was statistically highly significant(p value-0.001). Also type 2 diabetic patients' glycemic status was compared to helicobacter pylori infection by rapid urease test. According to their HbA1c levels they were divided into 3 groups of less than 7(good control), 7 to 9(poor control) and more than 9(bad control).using pearson chi square test the association of glycemia in all three groups was not statistically significant (p-value=0.254).There was a discordance between helicobacter pylori diagnosed by rapid urease test and by histopathology examination which was done by routine hematoxylin and eosin stain.(62/95 rapid urease test positive as compared to 50/95 by histopathology).

CONCLUSION

This study proves that the prevalence of helicobacter pylori is high in type 2 diabetic patients than non-diabetic patients with dyspepsia. Glycemic levels in Type 2 diabetic patients had no statistically significant correlation to Helicobacter pylori positivity by rapid urease test.

KEY WORDS: Helicibacter pylori, Type 2 Diabetes mellitus, Rapid urease test, Dyspepsia, HbA1c

INTRODUCTION

Helicobacter pylori infection remains one of the most common chronic bacterial infections in humans. Estimates suggest that more than half the world's population is infected with the bacterium and genetic sequence analysis proposes that humans have been infected for more than 58,000 years at a time when they first migrated from Africa.[1] Helicobacter pylori are unique bacteria ideally suited to live in the acidic environment of the human stomach. Their spiral shape and multiple unipolar flagella allow them to move freely through the gastric mucous layer, where they remain protected from low gastric pH.[2] Organisms produce large amounts of urease, an enzyme that hydrolyzes urea to alkaline ammonia and CO_2. This permits the bacteria to further control the pH of their microenvironment. Urease is also the basis of clinical diagnostic tests (urea breath test and rapid urea biopsy tests) for infection. H. pylori remain difficult and tedious to culture because they grow slowly and require specialized culture media and a controlled microaerophilic environment.

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on the etiology of the DM, factors contributing to hyperglycemia include

reduced insulin secretion, decreased glucose utilization, and increased glucose production. In Type 2 diabetes mellitus which has a genetic basis, there is insulin resistance as well as decreased production of insulin. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

The National Urban Diabetes Survey (NUDS), a population based study was conducted in six metropolitan cities across India and recruited 11,216 subjects aged 20 yr and above representative of all socio-economic strata. The study reported that the age standardized prevalence of type 2diabetes was 12.1 per cent. This study also revealed that the prevalence in the southern part of India to be higher-13.5 per cent in Chennai.[3]Various studies conducted in different parts of the world have given conflicting results regarding the association between Type 2 Diabetes mellitus and H.pylori.

Since there are only a few studies in our country on the association of Helicobacter pylori and Type 2 diabetes mellitus, we conducted this study in our institute.

REVIEW OF LITERATURE

Helicobacter pylori, which persistently colonizes the stomachs of ~50% of the world's human population, is the main risk factor for peptic ulceration as well as for gastric adenocarcinoma and gastric MALT (mucosa associated lymphoid tissue) lymphoma .Treatment for H. pylori has revolutionized the management of peptic ulcer disease, providing a permanent cure in many cases. The prevention of H. pylori colonization could potentially represent primary prevention of gastric malignancy and peptic ulceration.

EPIDEMIOLOGY

H. pylori have been demonstrated worldwide in individuals of all ages, infection is more common and acquired at an earlier age in developing countries compared with industrialized nations.[4,5] In developing nations, the majority of children become infected before the age of 10, and during early childhood spontaneous elimination of bacteria and subsequent reinfection is quite common. Infection persists in older children and adults so that in the developing areas of the world H. pylori prevalence can reach more than 80% by age 50. Spontaneous clearance often occurs and there is less chance of reinfection; thus, persistent childhood infection is much less frequently seen than in less-developed

countries.[4] In fact, serologic evidence of H. pylori is uncommon in children before age 10, but rises to 10% in adults between 18 and 30 years of age and further increases to 50% in those 60 or older.[4]

Especially in developing countries, contaminated water might serve as an environmental source of bacteria because the organism can remain viable for several days in water.[6] Bacterial deoxyribonucleic acid (DNA) can be found in samples of municipal water from endemic areas of infection but whether viable H. pylori are present remains to be proven.[7] In countries where infection is common, children who drink untreated stream water, eat uncooked vegetables, or swim in rivers and streams are more likely to harbour the bacteria, providing further indirect evidence of an environmental source of organisms.

Infected gastric secretions can serve as a source of bacterial transmission. Iatrogenic infection has occurred during the use of a variety of inadequately disinfected gastric devices, endoscopes, and endoscopic accessories.[8] Gastroenterologists and nurses appear to be at greater risk for acquiring H. pylori, presumably due to occupational contact with infected gastric secretions.[9] Mandated universal precautions, standardized equipment disinfection, and use of video-endoscopes that

reposition the instrument channel away from the mouth should reduce such iatrogenic and occupational transmission.

Natural transmission could occur through contact with infected vomitus during an acute illness[10] or with regurgitated material from an infected child

PATHOGENESIS

Specific genetic or phenotypic factors in infectious agents have been implicated as single causal factors in a variety of infectious diseases and associated outbreaks. However, H. pylori infection alone appears insufficient to fully explain the spectrum of diseases that is associated with chronic infection. Research over the past quarter century suggests that the pathogenicity of depends on bacterial and host factors in addition to less well-defined environmental conditions. Virulence of this infectious pathogen is based on bacterial properties that allow colonization and adaptation to the gastric environment and a host response that contributes to the host physiologic and histologic changes.

COLONIZATION AND VIRULENCE FACTORS

H. pylori show a strict tropism for the gastric mucosa or intestinal sites in which there is gastric metaplasia. H. pylori do not colonize

epithelium in the stomach that has undergone intestinal metaplastic change, possibly due to the production of antimicrobial factors that select against colonization. H. pylori rarely colonize the deeper portions of the gastric glandular mucosa, where O-glycans that impair H. pylori growth are found.[11] H. pylori decreases the expression of the antibacterial molecule, secretory leukocyte protease inhibitor,[12] thereby removing an element of the host response that would be detrimental to the persistent infection.

After H. pylori migrate to the gastric epithelium, the organism attaches to host cells and may damage them in order to obtain nutrients from the subsequent inflammatory exudate or transudate. A key interaction between the bacteria and gastric epithelium involves a segment of bacterial DNA referred to as the cag pathogenicity island (cag PAI).

Genes within the cag PAI encode proteins that provide a type IV secretion apparatus (i.e., cagE) that allows bacterial macromolecules to translocate into the host cell (i.e., cagA).[13] cag PAI plays an important role in the pathogenesis of gastritis in humans[13] because H. pylori bearing the cag PAI are associated with increased interleukin-8 (IL-8) expression and inflammation in gastric mucosal biopsy specimens and

increased IL-8 expression and apoptosis in vitro.[14] Human studies in which duodenal ulceration occurred more frequently in children carrying strains expressing cagE associated with higher levels of gastric IL-8[15] corroborate animal and in vitro studies.

Gastric acid secretion is a major function of the gastric mucosa that is regulated by a variety of neural, endocrine, and immune factors.[16] Elevated fasting and meal- or hormone-stimulated levels of gastrin are well documented in H.pylori infection, and there is evidence that gastrin expression is regulated by bacterial factors and cytokines. Expression of somatostatin, an acid-inhibitory peptide, is diminished in infected individuals as is duodenal bicarbonate secretion. The net effect of H.pylori infection on acid secretion is complex and varies depending on the duration and distribution of infection and presence of mucosal atrophy.

Secretion of mucus is also affected by H.pylori infection with decreased amounts of mucus and gastric mucosal hydrophobicity; these abnormalities reverse after eradication of infection. Epithelial barrier function is altered during H.pylori infection as a consequence of both direct effects of H.pylori and the accompanying inflammatory response

that collectively increase epithelial cell proliferation and programmed cell death.[17]

Viral antigens are presented to T cells when infected apoptotic epithelial cells overlie the Peyer's patch. Engulfment of H.pylori infected epithelial cells by phagocytes may also be an important mechanism by which H.pylori can activate the host response, and it has been shown that macrophages bind and then engulf gastric epithelial cells that undergo apoptosis due to infection.[17]

The catabolism of urea by urease provides CO_2, which rapidly neutralizes the bactericidal activity of the peroxynitrate by reacting with it to form $ONO\text{-}OCO_2$. Urease may favour bacterial colonization by neutralizing some host responses but this also enhances the nitration potential of $ONOO^-$ and may favour mutagenesis of host cell DNA.

Because Th1 cells cannot clear H.pylori, some other T cell subset may have to be stimulated in order to confer immunity. Studies in animal models indicate that protective immunity was induced by vaccines for Helicobacter spp. via Th cells other than Th1 cells, possibly including Th2 cells. The anti-inflammatory cytokines associated with Th2 cells or other regulatory subsets of Th cells can attenuate the pathogenic effects

of Th1 cells.[18] More direct evidence suggests that IL-4 can decrease gastritis, an effect that may be mediated by the release of somatostatin.[19]

As gastric responses can be modified by Th2 cells, the role of other T cell subsets, such as regulatory T cells (Treg), in the pathogenesis of disease associated with H.pylori infection is being addressed. Depletion of Treg in neonatal mice leads to autoimmune gastritis,[20] and infection with H.pylori alleviates autoimmune gastritis induced in neonatal mice.[21] This suggests that infection may stimulate a subset of anti-inflammatory T cells that impair excessive inflammation, which could otherwise lead to the spontaneous clearance of the organism, an effect that appears to occur in the human mucosa in response to H.pylori infection.[22]

Antibodies in the gastrointestinal tract are normally of the immunoglobulin A (IgA) isotype, which are highly adapted for mucosal protection, conferring protective immunity without activating complement and stimulating deleterious amounts of inflammation.

During infection with H.pylori the number of IgA producing cells increases. IgG and IgM are also detected, along with activated complement. It has been suggested that the level of autoantibodies in humans correlates with the severity of gastritis.[17] Local immune

complexes contribute to gastroduodenal inflammation and tissue damage during infection and may contribute to autoimmune gastritis.

Monoclonal antibodies that recognize H.pylori cross-react with human and murine gastric epithelial cells.[23] Adoptive transfer of these antibodies to recipient mice induces gastritis,[23] as does the transfer of B cells that recognize heat shock proteins from individuals with maltoma.[24] Anti-Le antibodies have been described in humans and occur independently of the Le phenotype of the host but they do not appear to be autoreactive. Autoantibodies induced in mice may recognize different targets within the gastric mucosa and even though they may cross-react with human gastric tissue, autoantibodies induced in humans may have a completely different specificity.

Infection with H.pylori persists for the life of the host unless there is some intervention with antibiotics. This observation has led to investigations as to whether immunity is impaired by immunologic avoidance or tolerance. Several bacterial factors, including catalase and urease, antagonize innate host responses. Production of the enzyme arginase by H.pylori inhibits NO production and may favour bacterial survival,[25] whereas virulent strains of H.pylori have also been shown to alter mucus production and phagocytosis.[26]

CONDITIONS ARISING FROM INFECTION

Infection of the human stomach by H.pylori leads to gastritis, which initially affects the superficial layers of the mucosa. In some instances the infection is short lived, but typically the infection results in a unique pattern of gastritis, so-called chronic active gastritis, which is essentially a lifelong condition. Chemokines induced by infection lead to a persistent acute inflammatory infiltrate with neutrophils and other cells (active inflammation) coexisting with cells characteristic of chronic inflammation (lymphocytes, macrophages). Most chronically infected individuals are asymptomatic with somewhere between 10% and 15% going on to develop peptic ulcer disease, gastric adenocarcinoma, and lymphoma of the gastric mucosa–associated lymphoid tissue

H.pylori organisms colonize only gastric-type epithelium within the human host and may colonize tissues outside the stomach when there is gastric metaplasia of the esophagus or duodenum, or in a Meckel's diverticulum. The pattern of colonization within the stomach appears to be an important determinant of H.pylori disease manifestations. It is unclear exactly what leads to duodenal ulcers associated with H.pylori infection, but it is thought that hyperacidity associated with antral

colonization leads to gastric metaplasia of the duodenum, which can then become colonized, leading to duodenal ulcer in some instances.

Distal gastric infection may also present with erosions and small ulcers in the gastric antrum, similar in appearance to lesions associated with anti-inflammatory drug use. Gastric ulcers and gastric adenocarcinoma occur more often when there is proximal colonization of the stomach (pan-gastritis), which results in injury to the gastric glands, leading to atrophic gastritis and associated hypo- or achlorhydria .

The burden of risk of gastric cancer is considered largely attributable to H.pylori infection, with cag PAI–bearing strains having a higher association with gastric cancer than cag PAI–negative strains. Given the burden of gastric cancer worldwide, the risk of infection seemingly outweighs the benefits in terms of the development of proximal gastrointestinal tract cancer.

NONGASTRIC DISEASES AND H.PYLORI INFECTION

Over the past two decades a large number of associations with nongastric diseases and H.pylori infection have been reported including Raynaud's, scleroderma, idiopathic urticaria, acne rosacea, migraines,

thyroiditis, and Guillain-Barre syndrome, but the data supporting an association for this group of conditions are weak or nonexistent.[28]

Associations that have somewhat better levels of evidence for an association include coronary artery disease, immune thrombocytopenic purpura,[29,30] and iron deficiency anemia[31] and for the latter two conditions, eradication of infection may be considered when other treatments have failed. The proposed mechanisms leading to these various conditions range from systemic immune reactions, cross-reactivity of bacterial and host proteins, and events secondary to gastric mucosal injury.

DIAGNOSIS

The American College of Gastroenterology published updated U.S. guidelines in 2007 that recommend testing for H.pylori only if a clinician is prepared to treat a patient with a positive test result.[32] Specific indications for testing include patients with active or documented history of uncomplicated or complicated peptic ulcer, early gastric cancer, or gastric MALT lymphoma. Testing for H.pylori is often recommended in younger patients with uninvestigated dyspepsia and no “alarm features” (i.e., early satiety, unexplained weight loss, dysphagia, recurrent

vomiting, family history of gastric cancer)[33] and in patients with functional dyspepsia (symptoms and negative endoscopy).[34]

However, the clinical and cost benefits of H.pylori in the setting of dyspepsia remain controversial, especially in regions where prevalence of infection is relatively low and gastroesophageal reflux disease (GERD) as a cause of symptoms is high.[35] Testing for infection prior to starting nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce subsequent ulcers, but this not generally recommended or often done in the United States, where prevalence of *H. pylori* is low.[32]

Also there is no general recommendation to test asymptomatic persons, with the possible exception of those with a family history of gastric cancer,[36] particularly individuals of Asian, Eastern European, or Mesoamerican descent, for whom the risk of gastric malignancy is highest. Occasionally immune thrombocytopenic purpura[30,37] and refractory iron deficiency anemia[31] respond to eradication of infection, so decisions to test for H.pylori in these conditions are made on a case-by-case and regional basis.

Indications for Testing and Treatment of Helicobacter pylori Infection:

Supported by evidence

Active peptic ulcer disease (gastric or duodenal ulcer)
Confirmed history of peptic ulcer (not previously treated for H.pylori infection)
Gastric MALT-lymphoma (low grade)
Following endoscopic resection of early gastric cancer
Uninvestigated dyspepsia (if H.pylori population prevalence high)

Controversial
Functional dyspepsia
GERD
Persons using NSAIDs, especially when first initiating NSAID treatment
Unexplained iron deficiency anemia or immune thrombocytopenic purpura
Populations at higher risk of gastric cancer (e.g. Asians, Eastern Europeans, Mesoamericans)

There are endoscopic and non endoscopic means to diagnose infection, and techniques can directly (histologic demonstration of organisms, presence of bacterial antigen in the stool, culture) or indirectly (using urease or an antibody response as a marker of bacteria) detect H.pylori.[38,39] The appropriate method to choose depends on the clinical

situation, population prevalence, and pre-test probability of infection as well as test availability and cost. In addition, recent use of antibiotics or proton pump inhibitors can influence results of certain tests.[32]

DIAGNOSTIC TESTS FOR *HELICOBACTER PYLORI*

NONENDOSCOPIC TESTS	**ADVANTAGES**	**DISADVANTAGES**
Serology (qualitative or quantitative immunoglobulin G [IgG])	Widely available, inexpensive, good NPV	Poor PPV if HP prevalence is low, not useful after treatment
Urea breath test (^{13}C or ^{14}C)	Identifies active infection, accuracy (PPV, NPV) not affected by H. pylori prevalence, useful both before and after treatment	Availability and reimbursement inconsistent, accuracy affected by PPI and antibiotic use, small radiation dose with ^{14}C test
Stool antigen test	Identifies active infection; accuracy (PPV, NPV) not affected by H. pylori prevalence; useful both before and after treatment (monoclonal test)	Fewer data available for polyclonal test, accuracy affected by PPI and antibiotic use

ENDOSCOPIC TESTS	ADVANTAGES	DISADVANTAGES
Histology	Excellent sensitivity and specificity, especially with special and immune stains; provides additional information about gastric mucosa	Expensive (endoscopy and histopathology costs), interobserver variability, accuracy affected by PPI and antibiotic use
Rapid urease test	Rapid results, accurate in patients not using PPIs or antibiotics, no added histopathology cost	Requires endoscopy, less accurate after treatment or in patients using PPIs
Culture	Specificity 100%, allows antibiotic sensitivity testing	Difficult and tedious to perform; not widely available; expensive
Polymerase chain reaction (PCR) assay	Excellent sensitivity and specificity, permits detection of antibiotic resistance	Not widely available; technique not standardized; expensive

Performing endoscopy solely to diagnosis H.pylori infection is not appropriate; there are three methods—biopsy urease test, histology, and (less often) culture—to identify the organism during an otherwise indicated endoscopic procedure. The choice of method depends on the clinical situation, cost, and test accuracy.[32]

Guidelines propose initially using a biopsy urease test because the method is quick, easy to perform, relatively inexpensive, and generally

accurate. Gastric biopsy material is tested for urease activity by placing several pieces of tissue in a medium containing urea and a pH reagent. Bacterial urease hydrolyzes urea-liberating ammonia, producing an alkaline pH and a resultant colour change of the test medium.[38] Test results are often positive within minutes to hours.

Several urease test kits are commercially available based on the methodology described here, differing only with regard to medium (agar gel or membrane pad) and testing reagents.[38] These test kits are generally inexpensive but there are added costs associated with obtaining gastric tissue samples, for example, up-coding diagnostic esophagogastroduodenoscopy (EGD), to EGD with biopsy. Nevertheless, biopsy urease testing is less expensive than histology so one proposed cost-saving measure is to obtain specimens for histology but delay sending them to the laboratory pending urease test results. Specificity of the urease tests is 95% to 100% with false-positive tests uncommon.[38,40]

Although reported sensitivity of urease tests is 90% to 95%, accuracy can be negatively affected by blood in the stomach,[41] and current or recent use of medications such as antibiotics, bismuth-containing compounds, or acid inhibitors, especially PPIs.[42] Therefore, a negative urease test does not necessarily exclude H.pylori infection in an

individual taking antisecretory medication, a common scenario in patients referred for endoscopy. Testing samples from multiple regions of the stomach or stopping offending medication and delaying endoscopy for several weeks may improve test sensitivity in such patients.

Evaluation of gastric mucosal histology is generally not necessary to diagnose H.pylori, but it can provide information regarding the activity and severity of mucosal inflammation. Histology can also detect metaplasia, dysplasia, and neoplasia.[38] In addition to biopsying "clinically suspicious" areas, taking multiple biopsies and sampling lesser and greater curvatures of gastric antrum and body are important, especially when looking for evidence of multifocal atrophic gastritis and/or intestinal metaplasia . Histologic examination had been considered the gold standard for identifying infection, with reported sensitivity and specificity as high as 95% and 98%, respectively.[43]

However, the distribution and density of organisms can vary within the stomach resulting in sampling error, particularly in patients taking antisecretory medications.[32,38] Detecting organisms can be difficult when standard hematoxylin and eosin staining is used alone, but is less of an issue when processing tissue with special stains such as Giemsa, silver, or Genta or specific immune stains.[39,44]

H.pylori are difficult to culture because the organism is fastidious, slow growing, and requires specialized media and growth environment.[38,39] In fact the initial isolation of H.pylori occurred by happenstance when plated cultures incubated over a long holiday weekend. When culturing for H.pylori, tissue should be obtained before biopsy forceps become contaminated with formalin and placed in a container with only a few drops of saline to preserve the specimen during transport to a local or offsite microbiology facility.[39]

Although culture is not generally recommended, in those with refractory disease culture with antibiotic sensitivity testing can guide subsequent treatment, although in vitro sensitivity testing does not always predict clinical treatment outcome.[39,45]

Most often nonendoscopic tests are used to diagnose H.pylori infection, and serology remains the most popular method used, although use of other non-invasive methods that can detect active infection has increased. Infection incites a systemic immune response, and enzyme-linked immunosorbent assay (ELISA) technology can detect IgG antibodies to a variety of bacterial antigens in serum samples.[38,39]

Tests for IgA and IgM class antibodies are less reliable and not recommended.[38] Office-based kits that test whole blood can provide

results within 30 minutes and permit “point of service” testing. Although serology is inexpensive, non-invasive and ideally suited to a primary care setting, the prevalence of H.pylori in the population being tested influences its accuracy.[32] The sensitivity of serology is generally quite high (90% to 100%) but specificity is variable (76% to 96%), especially if prevalence of H.pylori is low. Therefore, in places where infection is less common (most areas of the United States), the negative predictive value of serology is high. On the other hand, the corresponding positive predictive value is poor, suggesting most often positive results are actually falsely positive.[32]

So it is best to confirm positive serology results with another method such as a stool antigen or urea breath test before starting treatment or to use a test that detects active infection in the first place. Conversion of a positive serology to negative after treatment suggests bacterial cure, but in most instances serology remains positive for months to years even after successful treatment of infection.[46] This “serologic scar” effectively precludes use of serology to confirm bacterial eradication after treatment, a practice that is unfortunately still quite common in the primary care setting even though better tests to confirm eradication are more widely available.

The urea breath test (UBT) detects active H.pylori infection and so it is useful for making the primary diagnosis, confirming the accuracy of serology, and documenting successful treatment.[32] UBT relies on bacterial hydrolysis of orally administered urea tagged with a carbon isotope, either 13C or 14C . Hydrolysis generates ammonia and tagged CO_2, which can be detected in breath samples.[38,39] The 13C test is best for children and pregnant women because it uses a nonradioactive isotope, whereas the radiation dose with the 14C test is 1 microCi[39] equivalent to one day of background radiation exposure.

The specificity of UBT is more than 95%[32]; therefore, false-positive results are uncommon. The sensitivity of the test is 88% to 95% with false-negative results reported in patients taking antisecretory therapy such as PPIs,[32,42] bismuth, or antibiotics. To improve accuracy, antibiotics should be stopped at least four weeks and PPIs at least one week before breath testing.[32] UBT is not accurate in patients who have had gastric resective surgery.

An immunoassay that detects the presence of bacterial antigens in stool of infected patients is an alternative nonendoscopic method to diagnose active H.pylori infection as well as confirm eradication following treatment. Overall sensitivity and specificity of the stool test

are comparable to the UBT (94% and 97%, respectively).[39,41] A rapid H.pylori stool antigen test is available that permits testing during a clinic visit but it is slightly less accurate than a traditional laboratory based stool test.[47]

The sensitivity of stool testing is negatively affected by PPIs, bismuth, and antibiotics, which can decrease bacterial load, so similar precautions as described earlier for UBT are appropriate when using stool tests.[39,42]

Polymerase chain reaction is a sensitive method to detect H.pylori in gastric mucosal biopsies, but it is not practical for routine clinical diagnosis. It is, however, used for research purposes to identify bacteria when ordinary culture is difficult, as when testing stool or drinking water in a community setting, to type organisms during epidemiologic or transmission studies or for “real time” antibiotic resistance testing of tissue.[48]

Current recommendations for testing are as follows. A stool antigen assay or UBT is the preferred non-invasive method for initial diagnosis of H.pylori because it can detect active infection. Serology is only useful to exclude H.pylori infection, and positive serology results

should be confirmed by a test for active infection before starting treatment.

Endoscopic biopsy is suitable for patients undergoing a diagnostic endoscopy who are found to have an abnormality such as an ulcer or for those requiring endoscopy to follow-up a gastric ulcer or suspected MALT lymphoma. Biopsy urease testing can be used in patients not taking a PPI or antibiotics when histopathology is not clinically necessary.

When clinically indicated it is appropriate to confirm successful eradication of infection with either a UBT or stool antigen test. These tests should not be performed sooner than four to six weeks after completion of treatment because earlier testing might yield false-negative results.

PPIs should be discontinued at least one week prior to testing to improve accuracy. Post-treatment endoscopy with biopsy is only necessary if a repeat procedure is clinically indicated to follow up complicated ulcer disease or other mucosal abnormality, but this should be delayed for at least four to six weeks after therapy. Sampling multiple areas of the stomach is important to avoid missing persistent infection because of density and distribution of bacteria by prior antibiotics and

concomitant antisecretory medications. Serology is not useful for follow-up because the test remains positive in most patients for months or even years after infection is gone.

TREATMENT

Because there is currently no “H.pylori specific” or single antibiotic available to cure infection, treatment requires combining several medications. Recommended regimens usually include two antibiotics dosed several times daily for 7 to 14 days along with acid-suppressive medication.[49] Attempts to simplify regimens or shorten treatment duration generally reduce effectiveness. Compliance can be a problem because taking multiple medications is difficult, and minor medication-related side effects are frequent. Treatment success can vary among countries and even within regions of countries, possibly related to antibiotic-resistant organisms that are more common than previously appreciated.[49,50] Despite these concerns, treatment regimens are available that cure H.pylori infection in more 75% of individuals.[51,52]

After cure, annual adult reinfection especially in developed countries is uncommon, probably less than 1%. Higher rates of reinfection are reported, but these often include cases that actually represent recrudescence of the original infection that failed to clear during

antibiotic treatment.[53] Reinfection tends to be higher in children especially after spontaneous clearance of a primary infection, and it is reported to be higher in adults living in areas of the world with high H.pylori prevalence.[54]

Triple therapy, composed of two antibiotics, Clarithromycin 500 mgs b.d. and Amoxicillin 1 gm b.d. along with a PPI for 7 to 14 days, is currently the most popular initial treatment for H.pylori. PPI triple therapy consistently cures more than 80% of infections, especially if organisms are sensitive to clarithromycin and longer treatment duration (14 or 10 days vs 7 days) is used. Metronidazole 500 mg b.d can be substituted for either amoxicillin or clarithromycin, but this is appropriate only for penicillin-allergic or macrolide-intolerant individuals because metronidazole resistance is common and can reduce treatment success.[32,49,51]

First-Line Treatment of Helicobacter pylori Infection

TREATMENT REGIMEN	DUR-ATION	ERADIC-ATION RATE	COMMENTS
PPI, clarithromycin 500 mg, amoxicillin 1000 mg (each twice daily)	10-14 days	70%-85%	Macrolide resistance affects eradication success; not appropriate for penicillin allergic individuals or those who have received a clarithromycin regimen in the past
PPI, clarithromycin 500 mg, metronidazole 500 mg (each twice daily)	10-14 days	70%-85%	Appropriate for penicillin-allergic individuals who have not received a clarithromycin-containing regimen in the past
PPI, amoxicillin 1000 mg (each twice daily) followed by PPI, clarithromycin 500 mg, tinidazole 500 mg (each twice daily)	5 days 5 days	90%	Appears highly effective despite clarithromycin resistance
Bismuth subsalicylate 525 mg, metronidazole 500 mg, tetracycline 500 mg (each four times daily) plus PPI or H_2RA (twice daily)	10-14 days	75%-90%	Inexpensive but complicated regimen; consider in penicillin allergic individual or if clarithromycin resistance is suspected; can be used for retreatment

A 10-day sequential regimen (a PPI and amoxicillin 1 g, each given twice daily for the first 5 days, followed by the PPI, clarithromycin 500 mg, and tinidazole 500 mg, each given twice daily for the remaining 5 days) improved overall eradication rates compared with standard PPI triple therapy (89% vs. 77 %), but was particularly better for clarithromycin-resistant bacteria (89% vs. 29%).[55] A pooled analysis of studies evaluating sequential therapy confirmed its superior efficacy especially with macrolide-resistant bacterial strains.[56] Such results are encouraging, although most experience with this treatment is geographically limited to Mediterranean countries. However, there is no reason to expect different efficacy in other regions.[55] Although used more than a decade ago, dual regimens consisting of a single antibiotic (amoxicillin or clarithromycin) and a PPI are no longer recommended because eradication is significantly less than with three drug regimens.[51]

Bismuth-based therapy, which combines a bismuth salt, metronidazole 500 mg and tetracycline 500 mg each given four times a day, and daily acid suppression (usually a PPI every day) for two weeks was actually one of the first therapies used to treat H.pylori. Although it remains effective (more than 80% eradication), the number of daily pills and associated frequent minor side effects negatively affect tolerability and compliance.

A combination capsule that contains bismuth subcitrate 140 mg, metronidazole 125 mg, and tetracycline 125 mg is available in the United States and Canada, simplifying bismuth-based treatment. In a comparative study, patients treated with three combination capsules four times daily and PPI twice daily for 10 days had comparable H.pylori eradication with those treated with traditional PPI triple therapy (88% vs. 83%).[57] Short course (1 to 7 days) bismuth-based treatment[58] has been evaluated, but consistent long-term cure of infection has not been confirmed, so abbreviated treatment cannot be recommended.[51]

Initial treatment of H.pylori infection fails in up to 25% of patients as a result of an infection with antibiotic-resistant organisms, poor compliance with medication, and patient demographics such as younger age, smoking, prior antibiotic use, and underlying condition (functional dyspepsia vs. peptic ulcer).[59,60]

A review of various retreatment regimens reported eradication rates of 46%, 70%, 80%, and 76 % percent for PPI dual therapies, PPI triple therapies, ranitidine bismuth citrate–based triple therapy and bismuth-based therapy, respectively.[61] Ranitidine bismuth citrate is no longer available in the United States. When two new antibiotics are used during retreatment, cure of infection appears to be superior compared

with when only one new antimicrobial is used. One more recently recommended “rescue therapy” includes a PPI, levofloxacin 250 mg, and amoxicillin 1 g, all given twice daily for 10 days. This combination cures infection in up to 80% of patients who have failed one or more prior treatment attempts.

Less well studied, but reported to be 85% effective when used as retreatment, is a combination of PPI and amoxicillin 1 g, each twice daily, along with rifabutin 300 mg every day for 10 days. A lower dose of rifabutin (150 mg) appears to be less effective. Successful retreatment with regimens substituting furazolidone for metronidazole has also been reported.

Rescue Treatment for Persistent Helicobacter pylori Infection

REGIMEN	DURATION	ERADICATION RATE	COMMENTS
Bismuth subsalicylate 525 mg, metronidazole 500mg, tetracycline 500 mg (each four times daily) **plus** PPI or H_2RA (twice daily)	14 days	70%	Inexpensive but complicated regimen, so compliance should be emphasized; less effective as retreatment than as initial therapy; full dose of metronidazole and two weeks of treatment appear necessary
PPI,amoxicillin 1000mg, levofloxacin 250 mg (each twice daily)	10-14 days	57%-91%	Limited data from the United States
PPI amoxicillin 1000 mg, rifabutin 150 mg (each twice daily)	14 days	60%-80%	Expensive; adverse hematologic events and drug interactions possible. Limited data from the United States

As initial treatment for H.pylori, a 10- to 14-day course of standard PPI triple therapy described previously (PPI, amoxicillin and clarithromycin) is recommended but a 10-day sequential regimen would be an appropriate alternative, especially if clarithromycin-resistant infection is suspected (see following). If infection persists after this treatment, bacteria are likely resistant to clarithromycin. Therefore, retreatment should be with one of the PPI triple regimens noted earlier that incorporates a different combination of medications or a bismuth-basedtherapy for 14 days.

Subsequent courses of treatment if necessary should also incorporate different antibiotic combinations when possible to lessen the effect of acquired antimicrobial resistance. Although selection of a treatment regimen based on antibiotic sensitivity testing might improve subsequent treatment results, this is not routinely recommended.

Primary resistance to antibiotics commonly used to treat H.pylori varies widely throughout the world.[49] In the United States resistance to metronidazole can be detected in up to 40% of stains, whereas clarithromycin resistance is approximately 11%. Resistance to tetracycline and amoxicillin is unusual, generally less than 1%.[62,63]

In the United States, clarithromycin and metronidazole resistance increase with age and are more common in women than in men. Clarithromycin resistance is more common in the mid-Atlantic and northeast regions of the country. Metronidazole resistance is more common in Hispanics and Asians.

Antibiotic resistance significantly affects the success of PPI triple regimens but is less important with bismuth-based regimens.[50] A bacterial point mutation(s) that prevents reduction of metronidazole to its active metabolite is responsible for drug resistance.[45] Resistance to metronidazole appears to be a relative condition that can be overcome in most instances by using a higher dose (500 mg) or combining the drug with a bismuth preparation. On the other hand, clarithromycin resistance appears to be an absolute situation that cannot be easily overcome by increasing the macrolide dose.

One of three bacterial point mutations within its conserved loop of 23S strand of ribosomal RNA (A2143G, A2142G, and A2142C) can interfere with ribosomal macrolide binding and lead to clarithromycin resistance.[45] The A2143G mutation appears to have the greatest negative effect on treatment and is likely the major reason for PPI triple therapy failure. Testing for specific mutations is not clinically available, so if

clarithromycin resistance is suspected or confirmed by culture, non-macrolide regimens or sequential therapy are appropriate treatment options.

Failed attempts at eradication generally result in secondary antibiotic resistance.[49] Therefore, one can assume when treatment with clarithromycin or metronidazole-containing regimens is unsuccessful, specific drug resistance has emerged which should influence any subsequent choice of therapy.[45]

Treatment-related side effects can occur in as many as 50% of patients taking one of the treatment regimens described previously, but generally these are mild and do not require discontinuation of therapy.

Some of the more common side effects include taste alteration and gastrointestinal (GI) upset with metronidazole and clarithromycin and allergic reactions and diarrhoea with amoxicillin. In addition, tetracycline should not be prescribed to children or pregnant women.

HELICOBACTER PYLORI AND TYPE 2 DIABETES MELLITUS

Infection with H.pylori is associated with increased levels of fetuin A and associated insulin resistance, which may be evidence of a link with diabetes, say researchers.

"Among the various factors capable of inducing insulin resistance, the up regulation of α2-Heremans Schmid glycoprotein, also known as human fetuin A, has been linked with impaired insulin sensitivity, glucose metabolism and, subsequently, the onset of diabetes mellitus," explain Spyros Potamianos (University of Thessaly, Larissa, Greece)

Certain pathogens increase levels of fetuin A. To investigate whether H.pylori is such an infection, levels of fetuin A were measured and fasting insulin and glucose in 105 non-diabetic patients who were undergoing esophagogastroduodenoscopy due to dyspeptic complaints.

As reported in the journal Diabetologia, 72 participants were found to be infected with H. pylori and 33 were not. In multivariate analysis (adjusted for age, gender, body mass index, lipids, and C-reactive protein), H.pylori positive individuals had significantly higher levels of fetuin A (0.74 vs 0.57 g/l) and homeostasis model assessment of insulin resistance (2.6-2.8 vs 1.9-2.0) than those who were not infected.

However, fasting glucose concentrations were similar between the two groups. Potamianos and team conclude that the "data from the present study are consistent with the notion that H. pylori infection may induce insulin resistance."

The authors caution that "the present model cannot be regarded as final, since it was shaped based upon the findings of a study of a more or less observational nature."

They conclude: "Further research is therefore required, preferably using a more 'mechanistic' approach so that the conclusions presented above may be verified, and perhaps expanded by the inclusion of other constituents, eg, adipokines, gastrin or somatostatin, before a widely accepted mechanism is completely established."

STUDY SHOWING INCREASED PREVALENCE OF HELICOBACTER PYLORI IN TYPE 2 DIABETES MELLITUS

1. Association between Type 2 diabetes mellitus and Helicobacter pylori infection. Bener A, Micallef R et al

Turkish Journal of Gastroenterology. 2007 Dec;18(4):225-9.

The aim of this study was to determine the association between Helicobacter pylori infection and Type 2 diabetes mellitus in the United Arab Emirates population. This was case control study comparing 210 type 2 diabetics and 210 non- diabetic subjects. H.pylori was found by histopathological examination by measuring antibody profiles among type 2 diabetes mellitus patients and the non-diabetic group.

The mean age of type 2 diabetes mellitus patients infected with Helicobacter pylori was 48.1 +/- 7.9 years compared to 46.7 +/- 5.4 years in the non-diabetic infected subjects. A positive antibody titer for Helicobacter pylori infection (IgA >or=300) was found in 76.7% of the diabetic subjects compared to 64.8% of the non-diabetic subjects ($p<0.009$). There was higher prevalence of H.pylori infection in diabetic obese patients than the non-diabetic subjects (23.6% vs 11.8%, $p<0.001$).This study suggested that there is a significant association between Helicobacter pylori infection and type 2 diabetes mellitus.

STUDY WHICH DID NOT SHOW ANY ASSOCIATION BETWEEN TYPE 2 DIABETES AND H.PYLORI

1. Prevalence of Helicobacter pylori infection in patients with diabetes mellitus

Ciortescu I, Sfarti C.et al Rev Med Chir Soc Med Nat Iasi. 2009 Oct-Dec;113(4):1048-55.

100 patients with diabetes mellitus type 1 and 2 (41 men and 59 women, mean age 58.59) were studied. Each patient did a self-report questionnaire to get information regarding the presence and severity of upper gastrointestinal tract symptoms. H. pylori status was confirmed by

serological test and histopathology study of gastric biopsy or 13C-urea breath test. Prevalence of H. pylori infection was found not to be significantly higher in diabetics than in controls (70% vs 73%). 49% H. pylori positive diabetics had type 2 diabetes mellitus, 27% had type 1 diabetes mellitus, with no statistically significant difference ($p > 0.05$).The authors found no statistically significant difference in the symptoms score between H. pylori positive and H.pylori negative diabetic patients. The main value of HbA1c levels in H. pylori--infected diabetics was 7.31% and 7.47% in H. pylori non-infected diabetics, without significant difference. The authors concluded that there was no statistically significant difference in the prevalence of H. pylori infection between diabetics and non-diabetics patients and no difference in the symptoms score between H. pylori positive and H. pylori negative diabetic patients. H. pylori in diabetics appears to have no influence glycemic status.

HelicotecUT®- rapid urease test.

HelicotecUT® is designed to detect the urease activity of Helicobacter pylori in gastric mucosal biopsies. H. pylori produce large amounts of the enzyme urease which exhibits the ability to hydrolyze urea into ammonium ion and bicarbonate. When a tissue specimen from a

patient is immersed in the HelicotecUT® test gel, the elevated pH level produced by the presence and activity of urease is indicated by a colour change of pH indicator in the test gel.

If the gel changes colour from yellow to pink or red, then the test of Helicobacter pylori is positive.

If the gel colour remains yellow after 24 hours, then the test is negative

AIM AND OBJECTIVES OF THE STUDY

- To determine the frequency of Helicobacter pylori (H. pylori) infection in type 2 diabetic and non-diabetic patients with dyspepsia

- To study the relationship between glycemic control and helicobacter pylori infection.

- To compare rapid urease test with histopathological examination of helicobacter pylori infection

MATERIALS AND METHODS

- This case-control study was carried out in our Department of

Digestive Health and Diseases (DDHD),Government peripheral hospital ,Chennai from October 2011 to February 2012.

- This is a hospital-based prospective case-control study conducted on 100 subjects who had dyspepsia as defined as pain or discomfort centered in the upper abdomen or bloating or vomiting or combination of any two symptoms.

- They were divided into two groups i.e. type 2 diabetics and non-diabetics; each group consisting of 50 patients.

- 100 patients between the age 25-60 yrs. with diabetes (50) and non-diabetics (50) were enrolled in this study.

- All non diabetic patients were subjected to Random blood glucose, blood urea, serum creatinine,liver function tests, ultrasound abdomen prior to gastroscopy whereas diabetic patients were subjected in addition to the above tests ,fasting and post prandial blood glucose , glycosylated haemoglobin tests.

- Helicobacter pylori testing by rapid urease test (helicotec UT, Strong biotech corp, Taiwan) and histological examination by antral and corpal biopsy done using gastroscopy.

- Ethical committee approval was obtained from Kilpauk medical college before starting the study.

- Written informed consent was obtained from all participating subjects in regional language (Tamil). Privacy was ensured.

- Statistical analysis was done by statistical analysis software SPSS (version 15.0) for windows.

The inclusion criteria of the study were:

(1) Dyspeptic patients above 25 years of age and below 60 years of age,

(2) Either gender,

(3) Patients with history of dyspepsia, bloating or vomiting for more than one month seen in our outpatient department (OPD),

(4) patients who were known cases of Type 2 diabetes mellitus and came with history of dyspepsia, vomiting, or bloating for more than one month.

The exclusion criteria of the study were:

(1) Patients of type-1 diabetes

(2) Non-cooperative patients who refuse to give consent or participate in the study

(3) Patients below the age of 25 years and above the age of 60 years

(4) Patients with gastric ulcer or erosions, duodenal ulcer or erosions, gastro oesophageal reflux disease and gastric malignancy

(5) Patients on glucosidase inhibitors

(6) Patients already treated for helicobacter pylori

(7) Patients on proton pump inhibitors or H2 receptor antagonists in the past six weeks prior to the study

RAPID UREASE TEST KIT USED IN THIS STUDY- HelicotecUT® PLUS

RESULTS AND STATISTICAL ANALYSIS

A total of 100 patients were recruited for this study (50 Type 2 diabetic patients and 50 non diabetic patients who acted as controls).

Of the 50 non diabetic patients, 2 had gastric ulcer and 1 had duodenal ulcer and were excluded from this study according to the exclusion criteria. Of the 50 diabetic patients, 2 patients had growth stomach and hence were excluded from this study according to the exclusion criteria. 47 patients were studied in non diabetic group and 48 in diabetic group ,totalling 95 patients. 55 patients were males (30 non diabetic and 25 diabetics). 40 patients were females (17 non diabetic and 23 diabetic). 74 patients had abdominal pain (non diabetic 36 and diabetic 38). 3 patients had abdominal bloating.

All were diabetics vomiting alone occurred in one non diabetic patient. 2 non diabetic patients had both bloating and vomiting. 4 non diabetic patients had abdominal pain and vomiting. 4 non diabetic patients had abdominal pain and bloating and 7 diabetic patients had abdominal pain and bloating. 26 patients were smokers (17 non diabetics and 9 diabetics).

21 patients consumed alcohol (15 non diabetics and 6 diabetics). 42 patients had fatty liver in ultrasound (10 non diabetics and 32 diabetics).

62 patients had Rapid urease test positive for helicobacter pylori (22 non diabetics and 40 diabetics). 50 patients had Histopathology positive for helicobacter pylori (16 non diabetics and 34 diabetics).

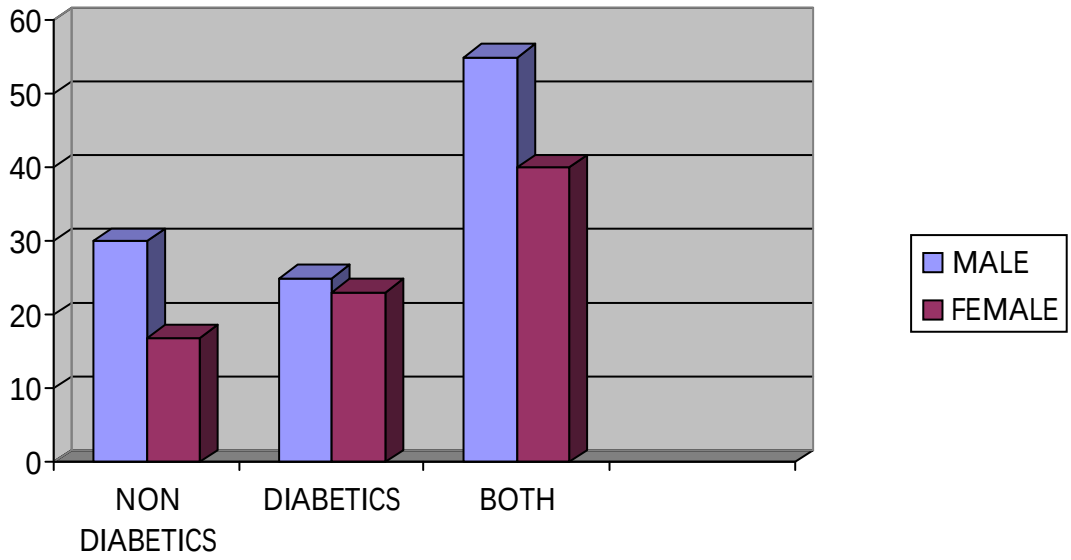
STATISTICAL ANALYSIS

Sex

Crosstab

			Group	
			Non-Diabetics	**Diabetics**
Sex	Male	Count	30	25
		% within Sex	54.5%	45.5%
		% within Group	63.8%	52.1%
	Female	Count	17	23
		% within Sex	42.5%	57.5%
		% within Group	36.2%	47.9%
Total		Count	47	48

P value – 0.246 (statistically not significant) using Pearson Chi-Square tests.



SYMPTOM ANALYSIS
Crosstab

			Group	
			Non-Diabetics	**Diabetics**
SYMPTOM ANALYSIS	A	Count	36	38
		% within HISTORY	48.6%	51.4%
		% within Group	76.6%	79.2%
	AB	Count	4	7
		% within HISTORY	36.4%	63.6%
		% within Group	8.5%	14.6%
	AV	Count	4	0
		% within HISTORY	100.0%	.0%
		% within Group	8.5%	.0%
	B	Count	0	3
		% within HISTORY	.0%	100.0%
		% within Group	.0%	6.3%
	BV	Count	2	0
		% within HISTORY	100.0%	.0%
		% within Group	4.3%	.0%
	V	Count	1	0
		% within HISTORY	100.0%	.0%
		% within Group	2.1%	.0%
Total		**Count**	**47**	**48**

A- ABDOMINAL PAIN

B- BLOATING

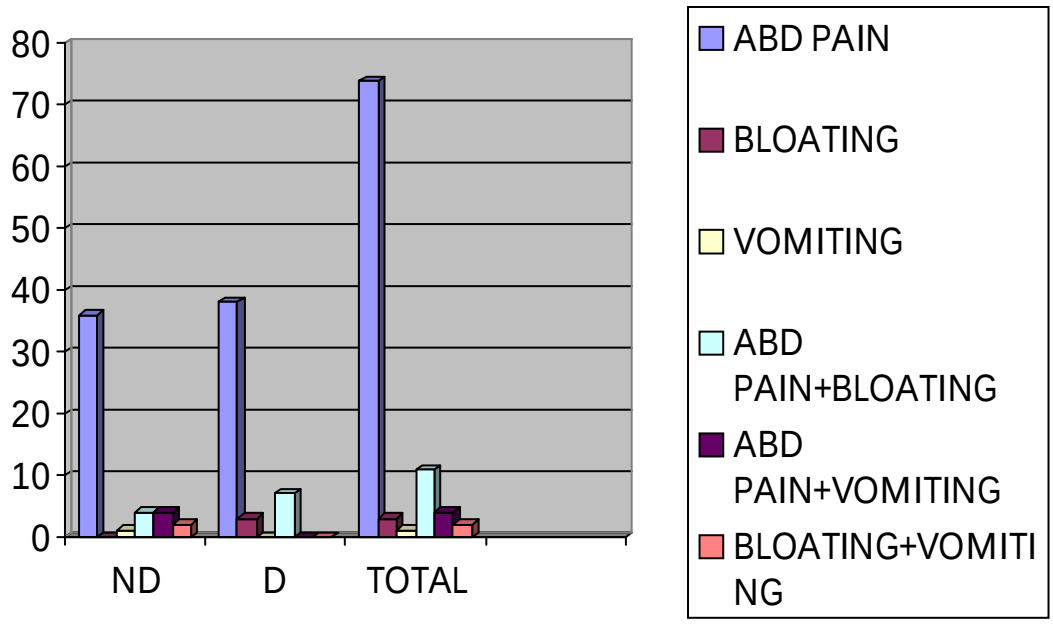
V-VOMITING

AV- ABDOMINAL PAIN AND VOMITING

AB- ABDOMINAL PAIN AND BLOATING

BV-BLOATING AND VOMITING

P value – 0.054 (statistically not significant) using Pearson Chi-Square tests.

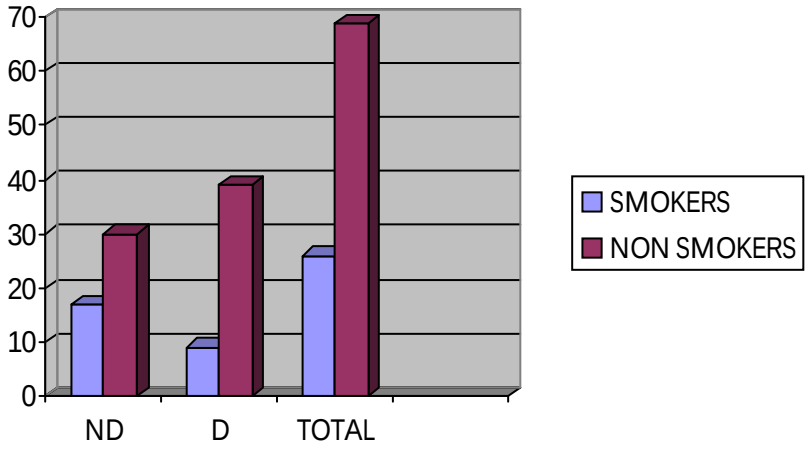


ND – NON DIABETICS
D – DIABETICS
SMOKING

Crosstab

			Group	
			Non-Diabetics	**Diabetics**
SMOKING	Yes	Count	17	9
		% within SMOKING	65.4%	34.6%
		% within Group	36.2%	18.8%
	No	Count	30	39
		% within SMOKING	43.5%	56.5%
		% within Group	63.8%	81.3%
Total		Count	47	48

P value – 0.057 (statistically not significant) using Pearson Chi-Square tests.



ND – NON DIABETICS

D – DIABETICS

ALCOHOL

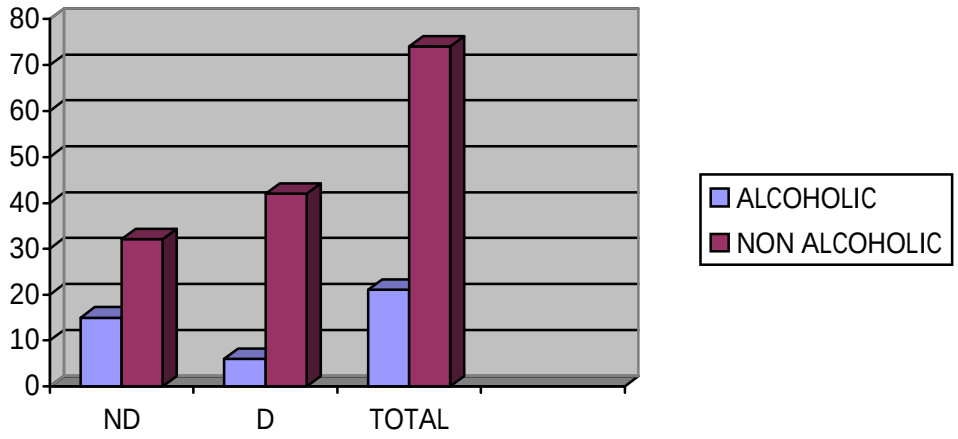
Crosstab

			Group	
			Non-Diabetics	**Diabetics**
ALCOHOL	Yes	Count	15	6
		% within ALCOHOL	71.4%	28.6%
		% within Group	31.9%	12.5%
	No	Count	32	42
		% within ALCOHOL	43.2%	56.8%
		% within Group	68.1%	87.5%
Total		Count	47	48

P value – 0.023 (statistically not significant) using Pearson Chi-Square tests.

ND – NON DIABETICS

D – DIABETICS



Ultrasound abdomen

Crosstab

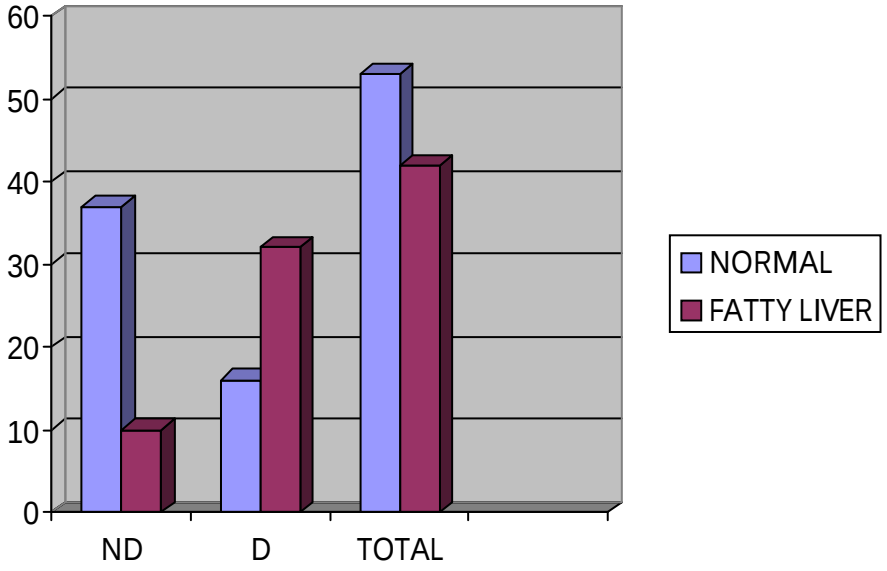
			Group	
			Non-Diabetics	**Diabetics**
USG	Normal	Count	37	16
		% within USG	69.8%	30.2%
		% within Group	78.7%	33.3%
	Fatty	Count	10	32
		% within USG	23.8%	76.2%
		% within Group	21.3%	66.7%
Total		Count	47	48

P value < 0.001 (statistically highly significant) using Pearson Chi-Square tests.

ND – NON DIABETICS

D – DIABETICS

RAPID UREASE TEST



Crosstab

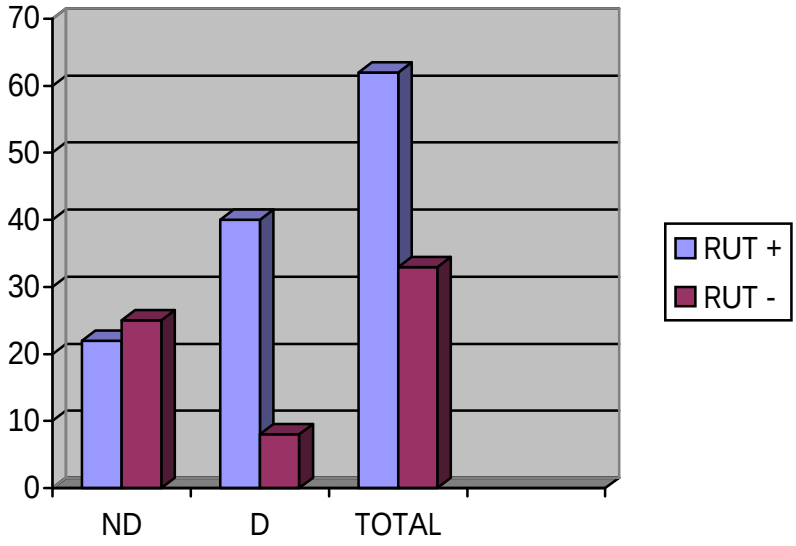
			Group	
			Non-Diabetics	**Diabetics**
RUT	Positive	Count	22	40
		% within RUT	35.5%	64.5%
		% within Group	46.8%	83.3%
	Negative	Count	25	8
		% within RUT	75.8%	24.2%
		% within Group	53.2%	16.7%
Total		Count	47	48

P value < 0.001 (statistically highly significant) using Pearson Chi-Square tests.

ND-NON DIABETICS

D-DIABETICS

RUT-RAPID UREASE TEST



Histopathology

Crosstab

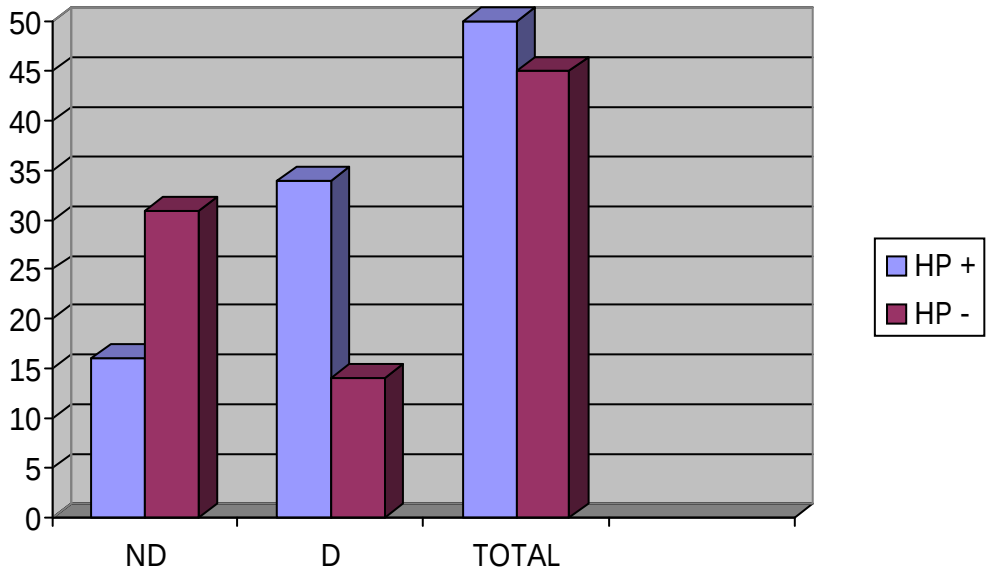
			Group	
			Non-Diabetics	Diabetics
HISTOLOGY	Positive	Count	16	34
		% within HISTOLOGY	32.0%	68.0%
		% within Group	34.0%	70.8%
	Negative	Count	31	14
		% within HISTOLOGY	68.9%	31.1%
		% within Group	66.0%	29.2%
Total		Count	47	48

P value < 0.001 (statistically highly significant) using Pearson Chi-Square tests.

ND-NON DIABETICS

D-DIABETICS

HP-HELICOBACTER PYLORI IN HISTOPATHOLOGY



Crosstabs

HBA1C * RUT

Crosstab

			RUT		P value
			Positive	**Negative**	
HBA1C	Upto 7	Count	6	0	0.254
		% within HBA1C	100.0%	.0%	
		% within RUT	15.0%	.0%	
	7-9	Count	24	4	
		% within HBA1C	85.7%	14.3%	
		% within RUT	60.0%	50.0%	
	Above 9	Count	10	4	
		% within HBA1C	71.4%	28.6%	
		% within RUT	25.0%	50.0%	
Total		Count	40	8	

P value – 0.0254 (statistically not significant) using Pearson Chi-Square tests.

FBS * RUT

Crosstab

			RUT		Total
			Positive	**Negative**	
FBS	Upto 100	Count	3	0	3
		% within FBS	100.0%	.0%	100.0%
		% within RUT	7.5%	.0%	6.3%
	100-140	Count	19	3	22
		% within FBS	86.4%	13.6%	100.0%
		% within RUT	47.5%	37.5%	45.8%
	Above 140	Count	18	5	23
		% within FBS	78.3%	21.7%	100.0%
		% within RUT	45.0%	62.5%	47.9%
Total		Count	40	8	48

P value – 0.557 (statistically not significant) using Pearson Chi-Square tests.

PPBS * RUT

Crosstab

			RUT	
			Positive	**Negative**
PPBS	Upto 140	Count	1	0
		% within PPBS	100.0%	.0%
		% within RUT	2.5%	.0%
	140-180	Count	9	0
		% within PPBS	100.0%	.0%
		% within RUT	22.5%	.0%
	Above 180	Count	30	8
		% within PPBS	78.9%	21.1%
		% within RUT	75.0%	100.0%
Total		Count	40	8

P value – 0.283 (statistically not significant) using Pearson Chi-Square tests.

DISCUSSION

Helicobacter pylori is a common infection in type 2 diabetics and these patients have colonisation of helicobacter pylori in the gastric antrum .This is probably because of certain chemotactic factors like tumour necrosis factor (TNF), interleukins like IL1, IL2, IL8 which are present in the gastric epithelium which do not confer protective immunity against helicobacter pylori but cause a number of changes in the gastric epithelium that promote inflammation and epithelial damage. The normal (helper T cell) TH1 cells boost cell mediated immunity to cancer and intracellular infection, TH2 cells seems more general and secretory immune response in mucosa. In helicobacter pylori infection TH1 cells predominate but TH2 cells are totally absent in Type 2 diabetic patients hence the helicobacter pylori infection is persistent.

The studies done to see the relationship between helicobacter pylori infection and Type 2 diabetes mellitus are few in number and have yielded mixed results. Few studies have reported a high incidence of between helicobacter pylori infection in Type 2 diabetics while others have failed to show the increased incidence of helicobacter pylori infection in dyspeptic patients with Type 2 diabetes mellitus.

Our study has shown an increased incidence of helicobacter pylori infection in Type 2 patients with dyspepsia as compared to non diabetic controls. Our study showed 40/48(83.3%) patients were rapid urease test positive for helicobacter pylori infection as compared to 22/47(46.8%) of rapid urease test positive for helicobacter pylori infection in non diabetic controls proving that infection with helicobacter pylori is increased in Type 2 diabetics with dyspepsia which was statistically highly significant(p value <0.001)

These results are comparable to a hospital based study done in Pakistan with 148 patients who were divided into two groups of Type 2 diabetics and non diabetics each having a sample size of 74 patients. They included all diabetic patients of age more than 35 years, both genders with a history of, epigastric pain or bloating for more than one month. Their analysis showed helicobacter pylori were positive in 54/74(73%) whereas in non diabetic patients' helicobacter pylorus was 38/74(51.4%). This study in concurrence to our study concluded that diabetic patients were more at risk of acquiring helicobacter pylori infection. [64]

There was another study which was conducted in Bikaner,rajasthan,India in 80 Type 2 diabetic patients . They studied the

association of helicobacter pylori and non gastrointestinal complication of Type 2 diabetes mellitus. They did gastroscopy and took gastric biopsy, used rapid urease test to demonstrate helicobacter pylori infection. They reported increased infection of helicobacter pylori in Type 2 diabetics.(p value-<0.05 statistically significant). [65]

However few other studies have shown a negative association of helicobacter pylori in Type 2 diabetics. In a study conducted in china, 63 type 2 diabetics were studied of which 29 had upper gastrointestinal symptoms. The control group was age adjusted non diabetic patients with dyspepsia. they did gastroscopy with antral mucosal biopsy and did rapid urease test(CLO TEST). Their results were that helicobacter pylori infection in Type 2 diabetics was 50.8% and in non diabetics was 56.4%.the statistical analysis was not significant. They reported that there was no association between helicobacter pylori infection, glycemic status, duration of disease and upper gastrointestinal symptoms.

In our study type 2 diabetic patients' glycemic status was compared to helicobacter pylori infection by rapid urease test. According to their HbA1c levels they were divided into 3 groups of less than 7(good control), 7 to 9(poor control) and more than 9(bad control).using pearson chi square test the association of glycemia in all three groups was not

statistically significant (p-value 0.254).Similarly Type 2 diabetics were grouped into 3 groups based on fasting and postprandial blood glucose levels. In fasting blood glucose the 3 groups were less than 100mg/dl,100-140mg/dl and more than 140 mg/dl and in postprandial blood glucose 3 groups were less than 140 mg/dl,140-180 mg/dl and more than 180 mg/dl and all were compared with rapid urease test for helicobacter pylori. But it did not show statistical significance. P-value FBS group (0.557) and PPBG group (0.283). hence we agree with the Chinese study that glycemic control does not correlate with helicobacter pylori infection inspite of the observation that helicobacter pylori was more common in type 2 diabetic patients. [66]

Another study done in Romania also showed that helicobacter pylori in diabetics had no correlation with glycemic status. They compared helicobacter pylori infection in both Type 1 and type 2 diabetics. They confirmed helicobacter pylori infection by serological test and histopathological examination of gastric biopsy or 13 C urea breath test. They showed 49% patients with Type 2 diabetics were positive for helicobacter pylori.

In our study there was a discordance between helicobacter pylori diagnosed by rapid urease test and by histopathology examination which

was done by routine hematoxylin and eosin stain.(62/95 rapid urease test positive as compared to 50/95 by histopathology).This discordance might be due to absence of routine use of special stains for staining helicobacter pylori like modified giemsa, silver stains etc., which might aid in diagnosing helicobacter pylori better. Hence we conclude that it is very advantageous for the gastroenterologist to use rapid urease test at endoscopy room to diagnose and treat helicobacter pylori early.

CONCLUSION

1. This study proves that the prevalence of helicobacter pylori is markedly high in Type 2 diabetic patients than non diabetic patients with dyspepsia.

2. Glycemic levels in Type 2 diabetic patients had no statistically significant correlation to helicobacter pylori positivity by rapid urease test.

3. Rapid urease test was more sensitive in diagnosing helicobacter pylori compared to routine histopathological examination.

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PROFORMA

Name of the patient:

Age:

Sex :

Occupation:

Phone number:

DDHD NO:

Address:

Clinical history:

Personal history

Smoking :
Alcohol:

Family history

Diabetes:
Hypertension:

Fasting blood glucose level:

Post prandial blood glucose level:

Hba1c:

Blood urea :

Serum creatinine :

Liver function tests:

Ultrasound abdomen:

MASTER CHART

Non diabetic patients

S.No.	DDHD NO	NAME	AGE	SEX	HISTORY	SMOKING	ALCOHOL	F/O DIABETES	F/O HT	RBS	UREA	CREAT-ININE	BILIRUBIN	AST	ALT	ALP	USG	RUT	HISTOLOGY
1	6242/11	JANAKIRAMAN	44	M	AB	Y	N	N	N	87	28	0.7	0.7	28	22	39	F	P	N
2	6916/11	PALANISAMY	42	M	AV	Y	Y	N	N	98	22	0.8	0.9	44	33	55	N	N	N
3	6769/11	MANI	55	M	A	Y	Y	N	N	117	29	0.7	0.3	38	32	43	N	P	P
4	6560/11	JEEVA	28	M	A	N	N	N	N	110	24	1.1	0.7	43	19	45	N	N	N
5	6581/11	PARVATHI	37	F	A	N	N	N	N	119	15	0.7	0.9	17	11	58	N	N	N
6	6111/11	GNANAVEL	39	M	A	N	N	N	N	121	17	0.9	1.1	18	20	77	F	P	P
7	6384/11	VELANKANNI	34	F	A	N	N	N	N	64	28	0.8	1	24	20	93	N	N	N
8	5691/11	SATHYAM	35	M	A	N	Y	N	Y	78	33	0.9	0.8	23	22	55	N	N	N
9	6723/11	SARASWATHY	39	F	A	N	N	N	N	88	21	0.7	0.8	19	19	58	N	P	P
10	7020/11	CHIDAMBARAM	48	M	V	Y	N	Y	N	122	27	0.7	0.9	17	34	111	N	P	P
11	7110/11	SIVA	22	M	A	Y	Y	N	N	98	22	1.2	0.5	34	34	98	N	N	N
12	3381/09	PARVATHY	45	F	A	N	N	N	N	112	34	0.8	0.7	25	22	77	N	P	P
13	7654/11	RAVI	42	M	A	N	Y	N	N	136	19	0.9	0.3	33	31	89	F	N	N
14	7537/11	MUNIRATHINAM	35	M	A	N	N	N	N	87	17	0.8	1	23	18	94	N	N	N
15	7188/11	SARAVANAN	46	M	A	Y	Y	N	N	97	33	0.7	1	25	44	88	N	P	P
16	7740/11	HUSSAIN	33	M	A	N	N	Y	Y	112	24	0.8	0.9	27	16	98	N	N	N
17	7169/11	KUPPUSAMY	50	M	A	Y	Y	Y	Y	111	25	0.9	0.7	19	16	77	N	P	P
18	6934/11	MALA	49	F	A	N	N	N	N	96	33	1.1	0.5	16	14	121	F	P	P
19	6318/11	GNANAPRAKASH	23	M	A	Y	Y	N	N	116	27	0.7	0.7	14	10	85	N	P	P
20	6863/11	CHANDRAN	50	M	A	Y	Y	Y	N	145	21	0.7	0.83	18	37	127	N	N	N
21	6777/11	HAMEED	32	M	AB	N	Y	N	N	105	25	0.6	0.31	42	36	47	F	P	N
22	6545/11	MEIYAMMAI	52	F	BV	N	N	N	N	110	28	0.7	0.9	19	22	37	N	N	N
23	6342/11	MANIBASHYAM	45	M	A	Y	N	N	N	122	34	0.6	0.5	17	17	98	F	N	N
24	7232/11	MANIVANNAN	55	M	A	Y	Y	N	N	98	26	0.6	0.3	37	32	77	N	N	N
25	6989/11	SURYA	34	F	AV	N	N	N	N	78	18	0.7	0.9	33	22	56	N	P	N
26	6453/11	VIJAYALAKSMI	54	F	A	N	N	N	N	88	22	0.7	0.8	35	26	67	N	N	N
27	7685/11	MARIAMMAL	44	F	A	N	N	N	N	113	26	1.1	0.7	22	27	99	N	P	P
28	7555/11	KAMALAM	56	F	A	N	N	N	Y	137	33	1.2	0.6	29	26	67	N	N	N
29	6983/11	VIMAL	44	M	A	N	N	N	N	143	34	0.9	0.5	30	18	111	N	N	N
30	6857/11	VINAY	26	M	A	N	Y	N	N	112	18	0.8	1	38	19	78	N	N	N
31	7564/11	MUNUSAMY	34	M	A	Y	N	N	N	143	17	0.7	1.1	24	20	76	F	N	N
32	7681/11	RATHINAM	33	F	AV	N	N	N	N	97	22	0.7	0.9	27	30	65	N	P	N
33	7932/11	RAMATHAL	43	F	AB	N	N	N	N	76	28	0.9	0.6	34	33	98	N	P	P
34	6565/11	KARTHY	27	M	AB	N	N	Y	N	78	32	0.8	0.4	34	43	75	N	N	N

S.No.	DDHD NO	NAME	AGE	SEX	HISTORY	SMOKING	ALCOHOL	F/O DIABETES	F/O HT	RBS	UREA	CREAT-ININE	BILIRUBIN	AST	ALT	ALP	USG	RUT	HISTOLOGY
35	7654/11	VIMALA	29	F	A	N	N	N	N	113	19	0.9	0.9	19	22	74	N	N	N
36	7641/11	MUTHU	44	M	A	N	N	N	N	142	33	0.7	0.7	18	21	87	F	P	P
37	6132/11	BALA	43	M	A	Y	Y	N	Y	153	22	0.7	1	22	19	96	F	P	P
38	7132/11	RAMU	36	M	A	Y	Y	N	N	123	19	0.9	0.8	20	22	75	N	N	N
39	7342/11	JEEVA	37	M	A	Y	N	N	N	133	24	1.1	0.7	27	27	56	N	P	P
40	7251/11	FATHIMA	33	F	BV	N	N	N	N	98	28	1.2	0.7	33	33	87	N	N	N
41	6712/11	JENCY	30	F	A	N	N	N	N	78	32	0.9	0.6	38	32	88	N	N	N
42	7932/11	GANESH	54	M	A	N	N	Y	N	132	23	0.7	0.9	26	22	99	N	P	N
43	7812/11	PAPPAMMAL	53	F	A	Y	N	N	N	88	19	0.9	1	26	28	66	N	N	N
44	6767/11	KOODESWARAN	33	M	A	N	N	N	N	76	17	0.8	0.4	19	27	68	N	P	P
45	7122/11	PALANIVE	23	M	A	N	N	N	N	88	22	0.8	0.3	17	19	99	N	P	P
46	7341/11	KANAMMAL	44	F	AV	N	N	N	N	132	24	0.7	0.7	27	20	44	N	P	N
47	6798/11	GOPU	55	M	A	Y	Y	N	N	138	18	0.7	0.9	33	40	57	F	N	N

MASTER CHART

Diabetic patients

S.No.	DDHD NO	NAME	AGE	SEX	HISTORY	SMOKING	ALC-OHOL	F/O DIABETE	F/O HT	FBS	PPBS	HBA1C	UREA	CREATININE	BILIRUBIN	AST	ALT	ALP	USG	RUT	HIST-OLOGY
1	6776/11	RAVI	41	M	B	N	N	Y	Y	95	136	8.8	33	1.1	0.6	55	22	66	N	P	P
2	6339/11	SRIDAR	43	M	A	N	N	Y	N	136	212	7.56	31	0.8	0.4	40	32	57	N	P	N
3	275/11	SELVI	30	F	A	N	N	N	N	111	245	8.5	34	0.8	0.8	33	26	84	F	P	P
4	6403/11	KANNAGI	38	F	AB	N	N	N	N	216	315	10.1	36	1	0.7	28	22	44	F	P	P
5	6633/10	MURALIDH	56	M	A	N	N	Y	N	180	286	8.85	23	0.7	1.1	16	11	63	F	N	P
6	7009/11	MANONMA	45	F	A	N	N	Y	Y	117	225	6.2	25	0.6	0.9	45	44	112	N	P	N
7	6578/11	RANI	50	F	A	N	N	Y	Y	211	300	9.8	34	0.5	0.3	58	50	43	F	P	P
8	6634/11	JEBIN	38	F	A	N	N	Y	N	146	215	9.4	33	0.3	0.4	54	33	44	F	P	P
9	6861/11	HARICHAN	58	M	A	N	N	N	N	112	212	7.9	41	1.1	1.2	33	28	67	N	P	P
10	7341/11	SUBASH	58	M	AB	N	N	N	N	113	188	6.9	27	1.2	1.1	24	16	88	F	P	N
11	7311/11	KANCHAN	55	F	A	N	N	Y	N	233	345	12.5	44	0.6	0.7	18	17	67	F	N	N
12	6233/11	ANEES	33	F	A	N	N	Y	N	221	289	11.5	34	0.6	0.7	22	23	55	F	N	N
13	6544/11	AKIL	37	M	A	Y	Y	Y	N	132	198	7.9	24	0.6	0.7	44	26	63	F	P	P
14	7891/11	SATHYA	39	F	AB	N	N	N	N	142	231	9	33	0.7	0.4	44	44	110	F	P	P
15	7733/11	VASANTH	44	F	A	N	N	N	Y	132	237	7.8	34	1	0.3	33	24	102	F	P	N
16	6565/11	SHEILA	42	F	A	N	N	Y	N	212	265	8.8	18	0.6	1	26	34	69	F	P	P
17	7782/11	MADASAM	33	M	A	Y	N	N	Y	200	342	9.5	33	0.5	0.6	28	18	80	N	P	P
18	7890/11	RAMESH	29	M	A	Y	Y	N	Y	112	165	6.8	34	0.9	0.4	19	33	71	F	P	P
19	6743/11	KASI	56	M	A	N	Y	Y	N	122	180	7	33	1	0.9	16	33	65	F	P	P
20	6567/11	MURUGAN	33	M	A	N	N	Y	N	237	288	8.88	25	1.1	0.8	22	36	77	F	N	N
21	7453/11	KUPPAN	57	M	A	N	N	Y	N	133	289	9.6	33	0.9	1.1	44	28	102	F	N	N
22	7890/11	KALINGA	56	M	A	N	N	Y	N	110	179	7.9	44	0.8	0.8	53	30	78	N	P	P
23	6211/11	NOOR BEG	44	F	AB	N	N	N	N	98	143	6.7	26	0.8	0.6	33	18	98	N	P	P
24	6542/11	KEERTHI	33	F	AB	N	N	N	Y	223	298	9.67	18	0.6	0.7	55	18	99	F	P	N
25	6790/11	GOPAL	29	M	A	Y	Y	N	N	122	177	7.4	19	0.7	0.4	34	54	45	F	P	P
26	6334/11	JEMI	34	F	A	N	N	Y	N	112	187	7.2	44	0.5	0.5	37	33	56	N	P	P
27	6733/11	JOHN	55	M	A	N	N	Y	Y	156	200	8.5	23	0.3	0.9	35	38	84	N	P	P
28	7851/11	SUMATHY	54	F	A	N	N	Y	Y	232	283	9.7	27	0.5	1	35	36	88	N	N	N
29	7382/11	JOSEPH	44	M	A	N	N	N	N	132	215	7.6	45	1.1	0.4	55	23	93	F	P	P
30	7680/11	SEKAR	48	M	A	N	N	Y	N	100	167	6.9	35	1	0.9	22	30	47	N	P	P
31	6744/11	SEMBA	45	F	AB	N	N	Y	N	123	168	7.71	33	0.7	0.6	18	45	44	N	P	N

S.No.	DDHD NO	NAME	AGE	SEX	HISTORY	SMOKING	ALCOH-OL	F/O DIABETE	F/O HT	FBS	PPBS	HBA1C	UREA	CREATININE	BILIRUBIN	AST	ALT	ALP	USG	RUT	HIST-OLOGY
32	6044/11	ROSYLN	55	F	B	N	N	Y	N	144	188	7.89	27	0.7	0.8	45	24	78	F	P	P
33	6977/11	AZMAL	44	M	B	Y	N	N	N	156	234	9.8	18	0.5	0.3	22	33	103	F	P	P
34	7844/11	AMBAL	44	F	A	N	N	N	N	132	212	7.6	20	0.9	0.9	35	45	111	F	P	P
35	7600/11	KAPIL	47	M	A	Y	N	Y	N	177	231	9	30	0.5	1.1	55	23	121	F	P	P
36	6722/11	AMBUJAM	56	F	A	N	N	N	N	214	299	9.67	33	0.6	0.9	34	36	77	F	P	P
37	7656/11	MANI	33	M	A	N	Y	Y	N	123	198	7.22	34	1.1	0.7	38	45	69	F	N	N
38	7731/11	MANGATH	40	F	A	N	N	Y	Y	123	226	8.4	22	0.5	0.6	46	44	95	N	P	P
39	7380/11	MAPILLAI	49	M	A	N	N	N	N	146	288	8.77	37	0.7	0.9	47	24	67	F	P	P
40	7390/11	ROSE	34	F	AB	N	N	N	N	265	313	11.2	33	0.5	0.9	35	33	77	F	P	N
41	6733/11	KANI FATH	27	F	A	N	N	N	N	255	377	12.3	28	0.6	0.3	22	43	88	F	P	P
42	6098/11	PANICKER	56	M	A	Y	N	N	Y	123	188	7.9	33	0.9	0.7	19	33	86	N	P	P
43	7999/11	MANI	44	M	A	Y	N	N	N	112	178	7.45	27	0.5	0.5	30	40	65	F	P	P
44	7556/11	ARUN	40	M	A	Y	Y	Y	N	102	167	7.44	35	0.7	0.9	40	20	77	F	P	P
45	7677/11	ANAND	36	M	A	N	N	Y	N	116	201	7.5	25	0.5	0.5	44	15	89	F	N	N
46	6444/11	INDIRA	54	F	A	N	N	N	N	213	311	8.98	33	0.4	1	37	56	100	F	P	P
47	7609/11	BABU	44	M	A	N	N	N	Y	266	344	9.33	18	0.7	1.2	38	33	57	N	P	P
48	7655/11	PICHAI	34	F	A	N	N	Y	N	143	213	8.44	40	0.5	0.9	19	45	78	N	P	P